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A Second-Generation Study of 427 Probands With Congenital Heart Defects and Their 837 Children

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Objectives. This study attempted to answer the question, Do mothers with congenital cardiovascular defects have more affected children than fathers with cardiac anomalies?

Background. In the 1950s to 1960s, concern was expressed about the safety of pregnancy in women with cardiac anomalies and the possibility of inheritance.

Methods. In a prospective study over 25 years, 236 women with cardiac defects were followed through pregnancy, and their 418 offspring were examined during their 1st 3 years. A high incidence of congenital cardiac malformations was noted. Then, a retrospective study of 191 men from the same clinic group and their total family (419 children) was performed to compare the incidence of affected children between the maternal study and this subsequent paternal study.

Results. Of 837 live children of these 427 probands, 14.1% (118) had a congenital heart defect (13.4% in the maternal study, 14.8% in the paternal study). There was no correlation with the surgical status of the proband. Concordance was somewhat greater among the children of affected mothers compared with those of affected fathers. Included in these studies were 31 high risk probands, 10 with genetic syndromes and 21 who had an affected sibling. Respectively, 53% and 41% of their children had cardiac anomalies, with a concordance >50%; three fourths of these children had moderate to severe anomalies.

Conclusions. The incidence of congenital heart defects in the children was not statistically different between the maternal and paternal studies. With removal of the high risk probands from the total study group, the risk of one affected parent having a child with a cardiac anomaly was 10.7%. Of the entire 837 children, only 7.5% had moderate or severe defects.

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In the early 1950s, shortly after surgical correction of patent ductus arteriosus and coarctation of the aorta and palliation of cyanotic patients with tetralogy of Fallot was possible, young women patients began to ask, "Is it safe for me to become pregnant?" and, "Could my child inherit my heart problem?" There was inadequate information to answer either question at that time. To that end, a prospective study of the outcome of pregnancy was commenced in the mid-1960s in such patients known to the principal investigator (R.W.). During the next 25 years, 236 women with cardiac defects were followed up through successful pregnancy, labor and delivery. Their 418 offspring were examined at birth and at specified intervals for the 1st 3 years to ascertain the incidence of congenital heart defects in these progeny. Because the rate of recurrence was higher than expected (1), a comparative study of the children of fathers with cardiac anomalies from the same group was undertaken. Of our male patients who had become fathers, 191 were reevaluated, and each of their 419 children was examined by the same pediatric cardiologist (R.W.). A total of 837 live born children, almost equally divided between the affected mothers and fathers, were evaluated, and the incidence of congenital heart defects was determined in a second-generation study of their 427 probands (Fig. 1).

Methods

Patient group. In 1947 a pediatric cardiac diagnostic service was established at the Yale Medical Center under the auspices of the Connecticut State Department of Health as a demonstration project of the U.S. Children's Bureau, directed by the principal investigator. Between 1947 and 1960, ~5,000 children were seen, 1,556 of whom had a cardiac malformation. In 1960 the administration of the clinic was transferred to the Yale University School of Medicine, Department of Pediatrics and the Yale-New Haven Hospital, with continued maintenance of records and continuity of care. From this clinic patients with congenital cardiovascular defects who reached adulthood were the subjects of these offspring studies, not selected by diagnosis or medical history. Their course represents the clinical outcome of the care recommended during their childhood years, which in most

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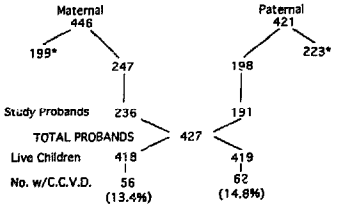

Figure 1. Study group. *Nonparticipants. No. w/C.C.V.D. = number with congenital cardiovascular defect.

instances was before the advent of open heart surgery. Some had corrective or palliative procedures, and others were considered to have such a mild defect that the risk of surgical correction was deemed inadvisable.

Table 1 identifies 849 of the 867 probands contacted, lists the proportionate composition of the 427 participants (236 mothers, 191 fathers) according to their diagnostic category and compares them with the 422 nonparticipants (199 women, 223 men). There was a significant difference between participants and nonparticipants with respect to the overall clinical distribution ($p < 0.02$), but the only individual diagnostic categories in which there were statistical differences were in the maternal conotruncal anomalies ($p < 0.02$), the fathers with patent ductus arteriosus ($p < 0.01$) and the small group of mitral valve anomalies. Mothers with conotruncal anomalies among the nonparticipants significantly outnumbered the participants ($p < 0.05$), in part due to fetal loss among those originally in the study and those possibly advised against pregnancy. Unexplained was the fact that we had so few participating fathers who had had a patent ductus arteriosus (although several were among the geographically inaccessible).

Maternal study. Preliminary planning for this prospective research began between 1962 and 1967. In 1968 a letter of invitation explaining the proposed study, together with a questionnaire, was mailed to the first 331 women seen in this clinic ≥18 years of age whom we were able to contact. Subsequently, 115 more were invited as they came of age. There was no attempt to select patients with specific malformations. The only requirement was that they had a congenital cardiovascular anomaly and were pregnant (1).

The plan was to follow the mother during the pregnancy, labor and delivery and to examine the infant periodically during the 1st 3 years to help answer the question of possible inheritance. Each woman was asked to contact the pediatric cardiologist (R.W.) early in the pregnancy if she was willing to participate. Of these 446 women, 247 (55%) responded and had a successful pregnancy, but 11 relocated during follow-up; thus, 236 (53%) completed this portion of the study (Fig. 1).

The cardiac status of the patient was reevaluated, and the family history of congenital or cardiac anomalies was updated. The interval history of the mother included her education, employment, illnesses, medications, the method of birth control, pregnancy history and habits, including the use of cigarettes, alcohol, drugs or teratogens before or during pregnancy. The progress of the pregnancy was monitored, including maternal illnesses, medications, obstetric or other complications, as well as cardiac status. The cardiologist worked closely with each patient's obstetrician, in many instances, members of the High Risk Obstetrical Service of the Yale-New Haven Medical Center. The principal investigator (R.W.) was usually present at the delivery. Apgar scores and a brief cardiac examination of the infant were recorded in the delivery room. Detailed physical and cardiovascular examinations and measurements of the infant were performed during the neonatal period and subsequently at 6 weeks, 6 months and 1 and 3 years of age. Child development evaluations were obtained at 9 months and 3 years at the Yale Child Study Center. Bone age was deter-

Table 1. Diagnostic Distribution of Congenital Cardiovascular Defects in Participants and Nonparticipants

	Participants			Nonparticipants		
Diagnosis	Maternal (n = 236)	Paternal (n = 191)	Total (n = 427)	Maternal (n = 199)	Paternal (n = 223)	Total (n = 422)
CT	8.9*	10.5	9.6†	15.5*	14.8	15.2†
PS	14.4	13.1	13.8	16.1	13.9	14.9
AS	8.0	17.8	12.4	10.4	14.8	12.6
COA	6.4	8.4	7.3	4.5	9.4	7.1
ASD	14.4	15.2	14.8	12.5	11.7	12.1
VSD	22.0	25.1	23.4	20.1	22.9	21.3
PDA	16.1	3.7‡	10.5	16.1	10.3‡	3.0
MVA	5.0	1.0	3.0†	1.0	0.9	0.9†
Misc	4.7	5.2	4.9	4.0	1.3	2.6

*$p < 0.05$, †$p < 0.02$ and ‡$p < 0.01$, participants versus nonparticipants. AS = aortic stenosis; ASD = atrial septal defect; COA = coarctation of aorta; CT = conotruncal anomaly; Misc = miscellaneous; MVA = mitral valve anomaly; PDA = patent ductus arteriosus; PS = pulmonary stenosis; VSD = ventricular septal defect.

mined by roentgenogram if there was a question of infant maturity. When there was any suspicion of a cardiac anomaly, an electrocardiogram, chest radiograph and echocardiogram (when this became available) were obtained.

Paternal study. The paternal study was performed from 1984 to 1989. Contact was made with 421 men with congenital heart defects seen in the clinic between 1947 and 1960. Of these, we found that 267 (43%) had fathered children, but 55 were geographically inaccessible, and 14 probands declined to participate. Of the 198 families remaining, data on seven families were incomplete because not all of the living children could participate in the examinations. Thus, of the 198 families seen, 191 had complete evaluations and were used for this study with their 419 children (Fig. 1).

Data obtained in the paternal study included the status of the proband, education, employment record, medications, smoking habits, use of drugs or alcohol, or both (the latter compared with the spouse's reply to these same questions). Information was procured from the mother of his child comparable to the data obtained in the maternal study. A family pedigree of proband and spouse was obtained with particular reference to cardiac or congenital anomalies. All fathers were carefully reevaluated and examined as well as the children. Electrocardiograms were obtained for all probands and children. If other studies such as echocardiograms were advisable in either parent or child, these were performed at the Yale Medical Center or at a pediatric cardiac center located near the respective family. These centers were very helpful, and most sent tapes of these studies for our own interpretation. Echocardiograms were read by two or more clinicians other than the investigator, one of whom was masked to any information concerning the request.

Classification of severity. All patients with congenital heart defects were categorized as having mild, moderate or severe anomalies. Those with mild anomalies (such as small ventricular defect or very mild pulmonary stenosis) had a normal life, had no cardiac enlargement, a normal ECG and no significant shunt or elevation of cardiovascular pressure, as determined by an echocardiogram. Those with moderate anomalies had defects that were not life threatening but had possible cardiac enlargement or moderate elevation of pressure or flow in one or more intracardiac chambers. Those with severe anomalies comprised children with a cardiovascular anomaly that caused either subjective symptoms or demonstrable cardiovascular dysfunction or was threatening because of abnormal flow or elevation of intracardiac or intravascular pressure. Such patients required cardiac catheterization or other procedures, or both, to determine the best course of immediate action.

Method of analysis. Chi-square analysis was performed throughout; significance was reported when $p < 0.05$. The Yates correction was used to calculate whether the observed frequencies were significant when the contingency tables were small.

Results

The maternal study included 236 probands with 418 live births; 56 of these infants (13.4%) had a congenital cardiac malformation. The paternal study included 191 probands with 419 children, 62 of whom (14.8%) had a cardiac anomaly. Combined, 427 probands had 837 children, 118 or 14.1% of whom were affected. There was no statistically significant difference between these two studies, and there was no correlation between the occurrence of cardiac defects in the progeny and any cardiac surgery in the proband before the birth of the child (Table 2).

In classifying the severity of the cardiac defect in the affected children 52 (47%) had a mild anomaly; 63 (53%) had a moderate or severe anomaly. A total of 17 children (14.4%) had severe defects, 16 of whom were the progeny of the 66 probands with severe anomalies. Thus, in the entire study of the 837 children, only 7.5% had moderate or severe cardiac defects.

Combined studies. The combined results that follow represent the entire group of probands and progeny seen in this study. Those who were at high risk with genetic syndromes or with strong family history will be addressed separately.

Table 2 lists the maternal and paternal probands according to the major classification of their cardiac malformations, the numbers of children born live and the number and percent of children who had a congenital cardiovascular defect. Each proband was listed only once.

Table 3 represents the number and distribution of congenital heart defects in the children according to the diagnostic category of the parent and also identifies concordance. Each asterisk in Table 3 represents one child with a severe malformation, of which there are 17. Concordant defects are discussed in the text, but the reader is referred to Table 3 for the presence of other defects.

Conotruncal anomalies. The probands in this group were equally divided by gender (21 female, 20 male). The most common malformation in this group was tetralogy of Fallot (16 mothers, 10 fathers). Transposition of the great arteries with pulmonary stenosis was present in two mothers and five fathers, truncus arteriosus in two mothers and one father, double-outlet right ventricle in one father and one mother; tricuspid atresia was present in one father and corrected transposition of the great arteries in two fathers.

Among the 11 affected children (15.7%) in this group, none had a conotruncal malformation. Component parts or forme fruste of this complex malformation, however, were present in four children with pulmonary stenosis and in one child with a ventricular septal defect that was interpreted as 45% concordance (Table 3). The only severely handicapped infant had a CHARGE syndrome with an ostium secundum defect, pulmonary stenosis and a retroesophageal subclavian artery.

Pulmonary valve stenosis. This group included 59 (34 mothers, 25 fathers) whose major diagnosis was pulmonary stenosis. Twenty-two (20%) of the 112 progeny had a cardiac

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Table 2. Congenital Cardiovascular Defects in Children of Affected Parents

	No. of Probands	No. of Living Children	CCVD	
			No.	%
CT				
Maternal	21	30	3 (2)	10 (6.7)
Paternal	20	40	8	20
Total	41	70	11 (10)	15.7 (14.3)
PS				
Maternal	34	60	10 (9)	17 (15)
Paternal	25	52	12	23
Total	59	112	22 (21)	19.6 (18.8)
AS				
Maternal	19	30	6	20
Paternal	34	80	11	14
Total	53	110	17	15.5
COA				
Maternal	15	26	3	11
Paternal	16	38	6	16
Total	31	64	9	14.1
ASD				
Maternal	34	57	4 (3)	7 (5.3)
Paternal	29	65	9	13.8
Total	63	122	13 (12)	10.7 (9.8)
VSD				
Maternal	52	91	18 (12)	20 (13.2)
Paternal	48	101	12	12
Total	100	192	30 (24)	15.6 (12.5)
PDA				
Maternal	38	84	8 (6)	9.5 (7.1)
Paternal	7	18	—	—
Total	45	102	8 (6)	7.8 (5.6)
MVA				
Maternal	12	23	—	—
Paternal	2	6	2	33
Total	14	29	2	6.9
Misc				
Maternal	11	17	4	24
Paternal	10	19	2	11
Total	21	36	6	16.7
Total				
Maternal	236	418	56 (45)	13.4 (10.8)
Paternal	191	419	62	14.8
Total	427	837	118 (107)	14.1 (12.8)

Numbers in parentheses are age corrected (11 infants with ventricular septal defect closed at the 3-year examination in maternal study). CCVD = congenital cardiovascular defect; other abbreviations as in Table 1.

defect with no significant difference in the incidence between the maternal or paternal offspring. Twelve of these children had pulmonary valve stenosis (55% concordance), severe in two and in one associated with a tricuspid valve malformation (Table 3).

Aortic valve stenosis. There were nearly twice as many fathers as mothers (34 and 19, respectively) who had aortic valve stenosis. The progressive nature of congenital aortic stenosis was very apparent in the reevaluation of these adult probands. In the paternal group, we saw the families of four fathers who had died (two of sepsis, two sudden deaths [one died the night before his scheduled operation]). Two men required urgent operation as a result of the reevaluation; two others had had valve replacement shortly before our reevaluation.

Four women had idiopathic hypertrophic obstructive cardiomyopathy, one of whom had had surgery at the National Institutes of Health, and a second had received propranolol during pregnancy—her infant was recognized as a cretin.

Cardiac defects were observed in 17 (15%) of the 110 children (Table 2). Aortic stenosis was present in eight of the affected children (42% concordance), with five of six being in the maternal study (Table 3).

Coarctation of the aorta. The gender distribution of the parents was nearly equal (15 and 16), and 30% (4 women, 7 men) had aortic stenosis as well. Three in each study had an associated patent ductus arteriosus. Two women became pregnant before surgical correction. Because of rapid increase in hypertension, one of them had successful repair with fetal monitoring during the 24th week of pregnancy (2).

Nine (14.1%) of the 64 children had a cardiac malformation, but none had coarctation of the aorta. It is a well known fact that many patients with coarctation of the aorta have aortic valve anomalies as well, which was the case in 10 of our 31 probands. Five (55%) of the nine affected children had aortic stenosis; in three of these the parent had aortic stenosis as well as coarctation of the aorta. Two of these children had severe aortic malformations, one with marked insufficiency associated with a bicuspid aortic valve.

Combining these left-sided obstructive deformities, the concordance was 50% (maternal 67%, paternal 41%). The highest concordance was among the children of mothers with aortic stenosis (83%) (Table 3).

Atrial septal defect. The 34 mothers and 29 fathers had 122 offspring, 13 of whom (10.7%) had a cardiac anomaly. None had conduction defects. Four of the 34 mothers had ostium primum defects; all seven children were normal. One mother had partial anomaly of the pulmonary venous return as well. The 29 remaining mothers had the usual ostium secundum defect, with four affected children: One child had a secundum defect, and of two children with a ventricular septal defect, one died after operation associated with a mitral valve deformity (Table 3). There was greater concordance among the children of the 29 fathers with an atrial septal defect (five [55%] of nine) than in the maternal study (one [25%] of four). Three fathers with ostium secundum defects had three children with the identical anomaly. Four fathers had an ostium primum defect, and of their seven children only one had the same defect. A father with a sinus venosus defect and partial anomaly of pulmonary venous return had a son with a secundum defect. The six parents with anomaly of pulmonary venous return had 13 children, 3 of whom were affected but had different defects. The overall concordance was 46% for all atrial septal defects (Table 3).

Ventricular septal defect. This represents the largest group, nearly equally divided between the mothers and

Table 3. Congenital Heart Defects in Children According to the Cardiac Defect in Parents

Proband	No. With CCVD	Diagnosis in Children (No.)									Concordance	
		CT	PS	AS	COA	ASD	VSD	PDA	MVA	MISC	No.	%
CT												
Maternal	3		1				1	1			2	67
Paternal	8		3*	2		3					3	38
PS												
Maternal	10		7**				3				7	70
Paternal	12	1*	5†	1*		2			2	1	5	42
AS												
Maternal	6		1	5							5	83
Paternal	11		3	3		2			3		3	27
COA												
Maternal	3			1			1	1*			1	33
Paternal	6			4**					2		4	66
ASD												
Maternal	4					1	2*	1			1	25
Paternal	9		1	2		5*	1				5	56
VSD												
Maternal	18 (12)		3			1*	12*	1*		1	12 (6)	67 (50)
Paternal	12		2	1		4	2		2	1	2	17
PDA												
Maternal	8		1			2*	2	3**			3	38
Paternal	0										0	0
MVA												
Maternal	0										0	0
Paternal	2								2		2	100
Misc‡												
Maternal	4		1	1			1	1*			0	0
Paternal	2		1							1	0	0
Total	118 (112)										55 (49)	47 (44)

*One severely affected child. **Two severely affected children. †One child has pulmonary insufficiency as well as aortic stenosis. Numbers in parentheses are corrected for ventricular septal defects that closed within the 1st 3 years in the maternal study. Abbreviations as in Tables 1 and 2.

fathers (52 and 48, respectively), with a total of 192 children. Eighteen affected children (20%) were seen in the maternal study, of whom 12 (66%) had a ventricular septal defect, six of which closed within the 3 years of follow-up examination. In the paternal study there were 12 children with a congenital heart defect, only 2 of whom had a ventricular defect (all were >3 years of age when seen; thus, some may have had defects that had already closed). Therefore, to determine concordance, only those who still had an open ventricular septal defect at age 3 years (6 of the mother's children) were considered and added to those 2 (of 12) in the paternal study. Thus, the total concordance for this defect was 8 (33%) of 24. In determining concordance, this then represented 50% of the remaining 12 affected children in comparison to the paternal study in which only 2 (17%) of 12 had a ventricular defect. Thus, the total concordance for this defect was 8 of 24, or 33% (Table 3).

Patent ductus arteriosus. Among the 38 mothers who had patent ductus arteriosus, 8 (9.5%) of their 84 children were affected, but only 3 had this same defect, and in none was it associated with prematurity. Because there were only seven fathers with no affected progeny in this group, the mother's risk of having an affected child seemed significantly greater than that of a father.

Mitral valve anomalies. Nonrheumatic mitral regurgitation was present in 12 women. Cardiac catheterization or echocardiograms, or both, indicated moderately severe prolapse of the mitral valve or severe mitral regurgitation, and 1 woman had moderately severe mitral stenosis. None of the 23 children of maternal probands was affected. Two of the paternal probands had moderately severe prolapse of the mitral valve. Of their six children, two sisters had the same defect with moderate mitral insufficiency, one associated with arrhythmias. Because these were the only affected children, the concordance was 100%, but the sample size was obviously small.

Miscellaneous. This group consists of five probands with an Ebstein-like malformation of the tricuspid valve (one of whom was male), three with serious aortic arch anomalies, seven with congenital arrhythmias (four with complete heart block) and two with dextrocardia without other significant deformities but with mild cardiac dysfunction. One woman had Uhl syndrome. The infant of one mother with a true Ebstein malformation had a small ventricular septal defect that subsequently closed by 2 years of age. Two women with apparently uncomplicated dextrocardia each had a child, one with mild aortic stenosis, the other with moderate pulmonary stenosis. The child of a father with an aortic arch

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Table 4. High Risk Probands

	No. of Probands	No. of Children	Children with CCVD		Concordance	
			No.	%	No.	%
Genetic						
Maternal	8	12	8	67	6	75
Paternal	2	3	0	0	—	—
Total	10	15	8	53	—	—
Familial						
Maternal	7	20	8	40	4	50
Paternal	14	26	11	42	6	55
Total	21	46	19	41	10	53

CCVD = congenital cardiovascular defects.

anomaly had a mild form of mitral insufficiency of unknown etiology. The daughter of a father with complete heart block had moderately severe pulmonary stenosis.

In this entire study, total concordance was 47% (55 of 118 children), with no statistical difference between the two studies. It was usual that maternal concordance was higher than that in the paternal study, except for coarctation of the aorta, atrial septal defect and mitral valve anomalies, when corrected for the closed ventricular defects in the maternal study, the concordance was 44%.

High risk probands. Most studies dealing with the occurrence of congenital heart defects in the children of affected parents have failed to take into account the possible higher recurrence rate in the progeny of those who had a genetic syndrome or a positive family history (Table 4).

Genetic syndromes. A genetic condition was found in 10 of our probands, 5 with hypertrophic obstructive cardiomyopathy, 3 with Noonan syndrome, 1 with Opitz syndrome and 1 with Uhl syndrome. Two of these were fathers whose 3 offspring had no defects, but of the eight mothers, 8 (67%) of their 12 children were affected, 6 (75%) with the identical syndrome.

In the Noonan syndrome group, two mothers and one father were affected. Although three of the mother's six children had pulmonary valve stenosis, only two (the second born in each instance) had the facial stigmata as well as the pulmonary valvular dysplasia typical of this syndrome.

Five parents had hypertrophic obstructive cardiomyopathy (or idiopathic hypertrophic subaortic stenosis). One father died suddenly before echocardiography; his father had died 2 years earlier of this same condition, proved at autopsy. His young daughter has no evidence of this problem to date. The four women in this group had six children, two of whom manifested early left-sided outflow tract hypertrophy, and one other had mild pulmonary stenosis.

One outstanding family history was that of a mother with Uhl syndrome, an Ebstein-like malformation. Two of her eight siblings had the same anomaly and had died at the ages of 19 and 23 years. Their autopsies confirmed the thin-walled, dilated right ventricle, with variable distortion of the tricuspid valve that had been found in all three at cardiac catheterization. The pregnancy of this one survivor was complicated by severe congestive failure (interruption of pregnancy had been refused) (3). She had been taking heroin and had a borderline rubella titer. Her infant was premature, small for gestational age and required surgical closure of a large patent ductus at 6 days of age. The child is severely mentally retarded, partially blind and totally deaf, suggestive of the rubella syndrome.

In summary, 10 probands with a genetic syndrome had 15 children, and eight (53%) were affected (six with moderate to severe defects) (Table 4).

Family history of congenital cardiovascular disease in first-degree relatives. In the review of family histories of first-degree relatives, the only information considered complete was that of affected siblings of the proband. In 21 of the 427 probands (5% of our population), a sibling had a cardiac anomaly. Among 46 progeny of these 21 probands, 19 had a cardiac defect: 8 (40%) of 20 in the maternal study and 11 (42%) of 26 in the paternal study.

In the conotruncal category, two fathers had an older sibling who died in infancy with the same defect as the proband, one with tetralogy of Fallot, the other with transposition of the great arteries. Of their four children, one had mild pulmonic stenosis, one had mild aortic stenosis, and two were unaffected.

One father with severe pulmonary valve stenosis had a daughter who had not only severe pulmonary stenosis but also an associated thickened tricuspid valve and an atrial septal defect. His second child had very mild pulmonary stenosis. This proband's sister (the paternal aunt) had died at 1 month of age with tricuspid atresia. Three more fathers with affected siblings had five children; the two affected belonged to one of these fathers.

Two fathers with aortic stenosis and with history of an affected sibling had five children, two of whom had aortic valve malformations, and one had pulmonic stenosis. There was no such family history of left-sided obstructions in the maternal study.

Two mothers with atrial septal defect each had a sister with patent ductus arteriosus. The first had two children with the same defects. Of the second pair, each sister had six pregnancies, but only the mother with the atrial defect had affected infants. She lost twins from the first pregnancy,

reported to have had multiple congenital anomalies with a possible trilocular heart, and her last child died at the age of 8 years at the time of repair of a ventricular septal defect with severe mitral valve involvement. Among the fathers there was no family history of significance.

One of the three women with a ventricular septal defect and an affected sibling had a child with an ostium primum defect comparable to that found in the maternal aunt; the other four children were unaffected. Four comparable fathers had two of seven children affected.

Two mothers with patent ductus likewise had affected siblings, but only one affected child. One father with a mitral valve anomaly whose brother had a prolapsed mitral valve had two normal children.

To summarize, these 21 probands with an affected sibling (representing 5% of our total study) had a 41% incidence of congenital heart defects in their progeny (19 of 46 children) (Table 4).

Single parent. What is the risk of one parent with a cardiac anomaly having a child with a heart defect if there is no family history of cardiac anomalies? To answer this question, all probands from these maternal and paternal studies, with a positive family history or genetic syndrome, together with their progeny, were removed from Table 1 (Table 5). There was then a significant difference ($p < 0.05$) between the parental studies in the atrial septal defect, patent ductus and mitral valve anomaly groups. Thus, 396 probands and 776 living children remained, of whom 83 (10.7%) were affected (8.3% in the maternal study, 13.1% in the paternal study). In this instance, using the correction for removing the ventricular septal defects that closed in the maternal study as before, the recurrence rate of congenital heart defects was significantly greater in the paternal probands ($p < 0.05$). The severity of defects in the affected children, however, in both of these parental studies was considerably less; ~50% were moderately or severely affected compared with the 75% who were more severely affected in the high risk families (Table 5).

Table 5. Congenital Cardiovascular Defects in Children of Affected Parents Without Genetic or Family History

	No. of Probands	No. of Living Children	CCVD	
			No.	%
CT				
Maternal	21	30	3*	10.0
Paternal	18	36	6	16.7
Total	39	66	9	13.6
PS				
Maternal	32	57	6*	10.5
Paternal	20	43	8	18.6
Total	52	100	14	14.0
AS				
Maternal	15	24	3	12.5
Paternal	31	74	8	10.8
Total	46	98	11	11.2
COA				
Maternal	15	26	3	11.5
Paternal	16	38	6	15.8
Total	31	64	9	14.1
ASD				
Maternal	32	49	0*	—
Paternal	28	64	9	14.0
Total	60	113	9	8.0†
VSD				
Maternal	48	84	9*	10.7
Paternal	44	94	10	10.6
Total	92	178	19	10.7
PDA				
Maternal	36	77	5*	6.5
Paternal	7	18	—	—
Total	43	95	5	5.3
MVA				
Maternal	12	23	—	—
Paternal	1	4	2	50.0
Total	13	27	2	7.4‡
Misc				
Maternal	10	16	3	18.8
Paternal	10	19	2	10.5
Total	20	35	5	14.3
Total				
Maternal	221	386	32	8.3
Paternal	175	390	51	13.1
Total	396	776	83	10.7†

*Excludes ventricular septal defects that had closed by age 3 years.
†$p < 0.05$. ‡$p < 0.02$. Abbreviations as in Tables 1 and 2.

Discussion

Our interest in the recurrence of congenital heart disease across generations began nearly 30 years ago when no data were available that could answer questions concerning the future expectations of a child with a congenital cardiac malformation. This question has since become of increasing importance as more and more patients survive childhood and adolescence to become parents. Recent advances in prenatal diagnosis have further accentuated the need for information that could guide the selection of families for genetic counseling, amniocentesis and fetal ultrasound to permit knowledgeable counseling and optimal management of pregnancy (4).

Recurrence risk. The original prospective pregnancy study of our female patients, published in 1982, reported a high incidence of congenital heart defects in the progeny of 233 affected mothers, with a recurrence rate of 16.1% without correction for ventricular septal defects that spontaneously closed and 14.2% after the exclusion of those with genetic syndromes or a family history of a cardiac anomaly (1). This occurrence rate was many times greater than the reported prevalence of cardiac malformations among newborns in the general population, determined to be 8 in 1,000 total births (5,6); but more recent population-based studies of the Prospective Collaborative Perinatal Study that reported only cardiac defects confirmed by invasive and noninvasive diagnostic methods indicated a lower population prevalence of 3.5 (7) and 5.5 (8) in 1,000 live births.

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The results of our maternal parent–child study raised the obvious questions: Would affected fathers have the same or lower incidence of cardiac anomalies in their progeny? Our findings cast doubt on the risk estimate (3 in 100) suggested for families in which a proband was affected (9). The role of inheritance became a major concern to us.

Parent studies. Parent studies were rare at the time of our first report, but in the same year Czeizel et al. (10) reported the incidence of cardiac defects in the offspring of parents who had had surgery for cardiac anomalies and found this to be higher among the mothers than expected. Likewise Emanuel et al. (11) in 1983 and Rose et al. (12) in 1985 studied the children of patients with specific defects and found the higher incidence of congenital heart defects among the infants of these affected mothers to be 14.3% and 13%, respectively. These reports further stimulated us to study the male probands from the same years in our cardiac clinic.

Subsequently, Nora and Nora in 1987 identified the gender of their probands previously reported (13) and combined their data with those of other studies and also reported a higher incidence of congenital cardiac anomalies in the children of affected mothers than of affected fathers in eight malformations (14).

Our review of nine published studies in which male and female probands were designated (10–21), combined with data of the present study, accumulated 3,715 parents with their 8,080 offspring, of whom 375, or only 4.45%, had congenital heart defects. Although the methodology of collecting information and the accuracy of diagnoses varied in these earlier studies, there appeared to be a significant increase in the incidence of cardiac defects in the progeny of affected mothers over that of the fathers ($p < 0.02$), but the only diagnostic group that showed this significant gender difference was that with ventricular septal defects ($p < 0.01$). There was no significant gender difference in the parents in the other diagnostic categories.

For a complete genetic evaluation it is important to include defects of mild severity as well as those more severe. However, mild lesions may have been overlooked in some previous investigations. Also, possible lack of knowledge in the paternal families might have played a role in some of these older studies because we observed in our paternal study that only 30% of these parents knew that their child had a significant murmur, but 80% of parents whose child had a moderate or severe defect were informed.

Dennis and Warren (19) studied the families of patients with ventricular septal defects and right ventricular outflow tract obstruction, and such combinations, and found no significant difference in the incidence of affected children whether the mother or father had the cardiac defect. This was the result of our study as well.

Comparison of recurrence rates. The results of the Second National Heart Study of the Natural History of Congenital Heart Defects Study (NHS-2) likewise found no significant difference in the incidence of congenital heart defects in the progeny of their affected mothers or fathers (20).

Our recurrence rates are higher than those in the NHS-2 study and also in the studies reported by Nora and Nora (14) and others, particularly in the categories of aortic stenosis, pulmonary stenosis, ventricular septal defect (20) and tetralogy of Fallot (21). In most other studies, when the examinations were performed by the investigator reporting the study (1,10–12,16,19), the incidence of congenital heart defects was higher than originally reported (~10%) and more comparable to the current study, although more selective in the scope of cardiac defects.

Some theories. Familial occurrence of some cardiac defects and certain genetic facts began to appear in published reports 10 to 15 years after early surgical correction of the patent ductus arteriosus and coarctation of the aorta and subsequent palliation in tetralogy of Fallot. Many theories have been proposed. In our study, Mendelian autosomal dominant and recessive manifestations applied in many syndromes. Genetic liability is apparent in some families, consistent with a single gene defect.

Nora (22) has recently reviewed many concepts or traditional and nontraditional inherent patterns and discusses multifactorial, mitochondrial and cytoplasmic inheritance possibilities and much more, anticipating that with more genomic studies, more solutions will evolve. Hoffman (23) has reviewed multiple opinions and agrees that polygenic and environmental effects do not account for the findings and leans toward single gene defects altered by "random events."

Clark (24) proposed a classification based on the probable major changes by mechanism within the developing embryo rather than phenotype. This makes it easier to consider teratogenesis in the developing embryo, well described by Pexeider (25). The classification of Clark was used by Ferencz and colleagues (26–31) in the population-based Baltimore–Washington Infant Study (BWIS) of congenital cardiac malformations. This study, working retrospectively from the affected newborn infant to the family, has also identified parental as well as familial heart defects, documenting these according to the general categories of left- and right-sided obstructions, atrial and ventricular defects (the "flow" defects) and conotruncal and other cardiovascular anomalies (32). When the Clark classification is applied to our present study, the conotruncal anomalies remain the same, but when the "flow" defects are combined, our recurrence rate then becomes 12%.

Of particular interest to us is the observation of the high incidence of parental sibling involvement in the Baltimore–Washington Study (31), comparable to our observation of 41% risk in the offspring of probands who had an affected sibling. There might be some molecular abnormalities, such as chromosomal deletion in certain genes, that might have been caused by some toxic insult in previous generations.

Pyeritz and Murphy (33,34) explored the etiology and pathogenesis of cardiac anomalies according to the pathogenic mechanisms of Clark and further elucidated altered embryonic hemodynamics. They believe that simple reliance

on the "3% to 5%" recurrence risk is now inaccurate. All recognize that the role of genes will become better understood in the future with the rapid progress in molecular biology.

Conclusions. In a study of the second generation of parents once patients in a pediatric cardiac clinic, we found that the incidence of congenital cardiovascular disease in their offspring was higher than had been previously expected. There was no difference in the incidence of a cardiac anomaly in the children whether the mother or father was the proband. There was no correlation with the surgical status of the proband.

Although slightly >50% of the affected children had moderate or severe defects, they represented only 7.5% of the entire group of 837 children in this study. The majority of children with severe defects were the progeny of parents considered to have had moderately severe cardiac malformations.

High risk probands included those with genetic syndromes and parents who had an affected sibling. The combined incidence of defects in these children was almost 44%; two-thirds were concordant, but three-fourths had moderate to severe anomalies.

In families where the only person affected is one parent, the incidence of a cardiac defect in the child approximates 10%. (This portion of the study unexpectedly found a higher incidence among the children of affected fathers.)

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